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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Notificat	ion of Transmittal of International Examination Report (Form PCT/IPEA/416)
025304-0247	International filing date (day/m		Priority date (day/month/year)
International application No.	l e		14 November 2004 (14.11.2004)
DCT/US03/36120	13 November 2003 (13.11.200	<u> </u>	
PCT/US03/36120 International Patent Classification (IPC)	or national classification and it	•	22/567 and US Cl.:
IPC(7): A23J 1/00; C07K 1/00,14/00,1 422/50; 435/4,7.1,7.2,7.21,7.24,7.92,2			33/48,33/53,33/543,33/567 and US Cl.: 530/412,413
1PC(7): A23 1700, CC 17.24,7.92,2	.87.1,287.7,288.7; 436/314,316,	341,001=	
Applicant			
CIPHERGEN BIOSYSTEMS, INC.			1 Decliminary
	aramination report has	been prepared l	by this International Preliminary Article 36.
1. This international prelim	hary examination 104	nt according to	Article 36.
Examining Allinolity and	1 10 (1000-		1
- amm - relate o	of a total of 7 sheets, including	ng this cover sh	neet.
2. This REPORT consists of	n a total or y		t i and/or drawings
	annexes.	i.e., sheets of t	he description, claims and/or drawings or sheets containing rectifications made
This report is also a	accompanied by Attitude 1	this report and/	or sheets containing reculications made
which have been ar	nended and are the basis for	n 607 of the Ac	or sheets containing rectifications made deministrative Instructions under the PCT).
before this Authori	ty (see Rule 70.10 and beens		or sheets containing recurrences of the PCT).
		•	
These annexes consist of a total of sheets.			
3. This report contains indications relating to the following items:			
3. This report contains indications related a			
I Basis of the report			
II Priority and industrial applicability			
Non-actablishment of report with regard to novelty, inventive step and industrial approximation			
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IV Lack of unit	y of invention		ate, inventive step or industrial
N-seemed st	atement under Article 35(2) v	vith regard to n	ovelty, inventive step or industrial statement
V Reasoned st applicability	atement under Article 33(2) v ; citations and explanations s	upporting such	statement
VI Certain doc	uments cited		
VII Certain defe	ects in the international applic	cation	
VIII Certain obs	ervations on the international	application	
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		Date of comp	letion of this report
Date of submission of the dema	nd	1	
i		02 March 2005	5 (02.03.2005)
14 June 2004 (14.06.2004)			/)
iline address of the II	PEA/US	Authorized off	Janue Ford
Name and mailing address of the II	.	Leon Y Lum	Character, do
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P.O. Box 1450 Alexandria, Virginia 22313-145	o	Telephone No	. 571-272-1600
Form PCT/IPEA/409 (cover sheet)(July 1998)		O

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INTERNATIONAL PRELIME	

[International application No. PCT/US03/36120
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TO THE PORT	PCT/US03/3012
INTERNATIONAL PRELIMINARY EXAMINATION REPORT	
INTERNATION	
I. Basis of the report	
I. Basis of the report 1. With regard to the elements of the international application:* 1. With regard to the elements of the international application:*	
With regard to the elements of the international application as originally filed. the international application as originally filed.	
57 . 1 corintion: " Flad	
the description: pages 1-34 pages NONE as originally filed filed with the demand filed with the letter of	
pages NONE , filed with the	ander Article 19
the claims: pages 35-40 pages NONE pages NON	tement) united 72
pages 33-40 pages NONE pages NONE pages NONE pages NONE pages NONE filed with the demand filed with the letter of	
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language available of the	of international services
2. With regard to the language, an application was filed, the language in which the international application was filed, the language in which the international application furnished for the purposes the language of a translation furnished for the purposes.	tion (under Rule 46.5(6))
These elements were available the language of a translation furnished for the purposes the language of publication of the international application the language of publication furnished for the purposes.	tion (under Rule 48.3(b)). ses of international preliminary examination(under Rules ce disclosed in the international application, the
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the language of publication furnished for the purpose the language of the translation furnished for the purpose 55.2 and/or 55.3). 3. With regard to any nucleotide and/or amino acid sequence of the purpose of the language of publication furnished for the purpose of the language of publication furnished for the purpose of the language of publication furnished for the purpose of the language of publication furnished for the purpose of the language of the translation furnished for the purpose of the language of the translation furnished for the purpose of the language of the translation furnished for the purpose of the language of the translation furnished for the purpose of the language of the translation furnished for the purpose of the language of the translation furnished for the purpose of the language of the translation furnished for the purpose of the language of the language of the translation furnished for the purpose of the language of	ne basis of the sequence insuing.
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3. With regard to display examination was contained preliminary examination was contained in the international application in printed for contained in the international application in confided together with the international application in containing the containing to this Authority in written for the containing the con	inputer readable form.
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international application as a sha information recorded in con	en sequence issuage. I
The statement that the mountain	26
has been furnished. The amendments have resulted in the cancellation	Oi:
4. The amendments are pages NONE	
the description, pages NONE	to 90
the claims, Nos. Nos. Nos.	mendments had not been made, since they have been considered to go plemental Box (Rule 70.2(c)).** plemental Box (Rule 70.1(c)).** In Office in response to an invitation under Article 14 are referred to in a contain amendments (Rules 70.16 and 70.17).
the drawings, sheets of the arr	nendments had not been made, since the plemental Box (Rule 70.2(c)).** In the plemental Box (Rule 70.2(c)).** In the plemental Box (Rule 70.16 and 70.17). In the plemental Box (Rules 70.16 and 70.17).
This report has been established. as indicated in the Support the disclosure as filed, as indicated in the receiving	ng Office in response to an invitation water (Rules 70.16 and 70.17).
beyond the been furnished to the record	nort since they at not contain and annexed to this report.
5. This report the beyond the disclosure as filed, as indicated the beyond the disclosure as filed, as indicated the receiving the separate sheets which have been furnished to the receiving this report as "originally filed" and are not annexed to this report this report as "originally filed" and are not annexed to this report this report as "originally filed" and are not annexed to this report the separate sheet containing such amendments must be separate sheet the separate sheet sheet the separate sheet the separate sheet the separate sheet	plemental Box (Rule 70.2(c)). plemental Box (Rule 70.2(c)). ng Office in response to an invitation under Article 14 are referred to the ng Office in response to an invitation under Kules 70.16 and 70.17). sort since they do not contain amendments (Rules 70.16 and 70.17). e referred to under item 1 and annexed to this report.
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Form PCT/IPEA/409 (Box I) (July 1998)



Vertica No.	
International application No.	
DCT/US03/36120	

INTERNATIONAL PRELIMINARY EXAMINATION RELIGIOR	PCT/USU3/36120				
	step and industrial applicability				
III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability 1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or 1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or					
 The question whether the claimed invention appears to be novel, to be industrially applicable have not been and will not be examined 	in respect of:				
the entire international application,					
claims Nos. 32-44	·				
because:	1: A door				
the said international application, or the said claim Nos not require international preliminary examination (specify):	relate to the following subject matter which does				
the description, claims or drawings (indicate particular elenthat no meaningful opinion could be formed (specify):	nents below) or said claims Nos are so unclear				
the claims, or said claims Nos are so inadequately opinion could be formed.					
no international search report has been established for said	d claims Nos. 32-44				
 A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions: 					
the written form has not been turnished of does not comp-					
the computer readable form has not been furnished or does not	comply with the standard.				
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Form PCT/IPEA/409 (Box III) (July 1998)



International application No. PCT/US03/36120

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

INTERNATIONAL PREDIME	11 1:1:4
V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty	inventive step or industrial applicability;
	, 111, 02201
V. Reasoned statement under transcript such statement	
V. Reasoned statement under citations and explanations supporting such statement	-

V. Reasoned statement under Rule 66.2(a)(citations and explanations supporting su	ii) with regard to horoty, ich statement	
1. STATEMENT		YES
Novelty (N)	Claims NONE Claims 1-3,15-17 and 31	· NO
·		YES
Inventive Step (IS)	Claims NONE Claims 1-31	NO
		YES
Industrial Applicability (IA)	Claims 1-31 Claims NONE	NO
	Cimin	

2. CITATIONS AND EXPLANATIONS

Please See Continuation Sheet

Form PCT/IPEA/409 (Box V) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

ſ	International apprication No.
1	PCT/US03/36120

	Certain defects in the internation	al application
VII.	Certain defects in the inter-	

The following defects in the form or contents of the international application have been noted:

Claim 5 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: The instant claim is repeated.

Form PCT/IPEA/409 (Box VII) (July 1998)



International application No. PCT/US03/36120

Supplemental Box	fals proceeding boxes is not sufficient)
(To be used when the space	in any of the preceding boxes is not sufficient)

Claims 1-3, 15-18, and 31 lack novelty under PCT Article 33(2) as being anticipated by Hitomi et al (US 5,976,832), in V. 2. Citations and Explanations: light of Ilg et al (Biochemical and Biophysical Research Communications, 1996, 225:146-150).

Hitomi et al reference teaches a diagnostic assay kit and method for detecting the presence of at least one biomarker indicative of intra-amniotic inflammation in a sample of amniotic fluid, comprising the steps of mixing an adsorbent that binds at least one biomarker associated with intra-amniotic inflammation with a sample of amniotic fluid and then monitoring said mixture for binding between said biomarker and said adsorbent, and instructions for said steps (claims 1 and 16), wherein the adsorbent is an antibody immobilized on a solid substrate (claims 2 and 17), wherein the diagnostic assay is an ELISA (claims 3 and 18), wherein said calgranulin is calgramulin C (claims 15 and 31), by disclosing assay of CAAF1 in amniotic fluid on an ELISA plate for the diagnosis of inflammatory disease (column 21, line 55 to column 22, line 58, especially column 21, lines 56-61 and column 22, lines 45-58), wherein CAAF1 is calgranulin C, as disclosed by fig et al reference (page 146, 2nd full paragraph, line 7 and notation 4).

Claims 4-5 and 19-21 lack an inventive step under PCT Article 33(3) as being obvious over Hitomi et al (US 5,976,832), in light of Ilg et al (Biochemical and Biophysical Research Communications, 1996, 225:146-150), and in view of Krone et al (Analytical

Hitomi et al reference has been disclosed above, but fails to teach that the solid substrate is a probe, wherein said biomarker Biochemistry, 1997, 244: 124-132). is detected by laser desorption/ionization mass spectrometry, and wherein said adsorbent is immobilized on a probe.

Krone et al reference discloses a BIA core CM5 biosensor chip covalently derivatized with an antibody, wherein species detected during surface plasmon resonance (SPR) for biomolecular interaction analysis (BIA) is interfaced with MALDI mass spectrometry, in order to determine and distinguish between binding of multiple ligands by identifying species detected during SPRbased BIA (page 125, right column, 1st full paragraph to page 126, left column, 1st full paragraph).

It would have been obvious to one of ordinary skill at the time of the invention to modify the kit and method of Hitomi et al with a BIAcore CM5 biosensor chip covalently derivatized with an antibody, wherein species detected during surface plasmon resonance (SPR) for biomolecular interaction analysis (BIA) is interfaced with MALDI mass spectrometry, as taught by Krone et al, in order to determine and distinguish between binding of multiple ligands by identifying species detected during SPR-based BIA. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in immobilizing antibodies onto a BIAcore biosensor chip and using mass spectrometry, as taught by Krone et al, in the kit and method of Hitomi et al, since Hitomi et al teach the detection of antigens using antibody assays, and the BIAcore biosensor chip and mass spectrometry taught by Krone et al is one example of an antibody-antigen binding assay to detection antigens in a sample.

Claims 6-7 and 22-23 lack an inventive step under under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and in further view of Keene (US 5,541,291).

Hitomi et al and Krone et al references have been disclosed above, but fail to teach that said adsorbent is a hydrophobic

Keene reference teaches ELISA assays with surface functionalizing using hydrophobic amino acids, in order to allow adsorbent on a probe.

Form PCT/IPEA/409 (Continuation Sheet) (July 1998)



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1	International application PCT/US03/36120	į	: 175B)	
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It would have been obvious to one of ordinar, skill in the art at the time of the invention to modify the kit and method of attachment by hydrophobic bonding to plastic surfaces (column 9, line 65 to column 10, line 9). Hitomi et al and Krone et al, with ELISA assays with surface functionalizing using hydrophobic amino acids, as taught by Keene, in muomi et ai and krone et ai, will ELISA assays will surface inflictionalizing using hydrophobic adius, as langin by Keele, order to allow attachment by hydrophobic bonding to plastic surfaces. One of ordinary skill in the art at the time of the invention order to anow attachment by hydrophobic bonding to plastic surfaces. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in using hydrophobic amino acids to functionalize a plastic surface for ELISA assays, as would have reasonable expectation of success in using hydrophobic alimno acros to runcuonalize a plastic surface for ELISA assays, as taught by Keene, in the kit and method of Hitomi et al and Krone et al, since Hitomi et al and Krone et al teach ELISA assays, and a

plastic surface is one type of substrate in which to perform an ELISA assay. Claims 8-13 and 24-29 lack an inventive step under PCT Article 33(3) as being obvious over Hitomi et al (US 5,976,832), in light of Ilg et al (Biochemical and Biophysical Research Communications, 1996, 225:146-150), and in view of Heine et al (US 2,976,832)

Hitomi et al reference has been disclosed above, but fails to teach that the assay additionally tests for the presence of at least one defensin in said sample of amniotic fluid (claims 8, 10, 12, 24 26, and 28), wherein said defensin is HNP-1 (claims 9, 11, 13, 25, 6,174,664 B1).

Heine et al reference discloses that monoclonal antibodies to the defensins HNP1-3 can be prepared for an ELISA in 96-well plates in order to screen a pregnant patient for the presence of an intraamniotic infection using amniotic fluid (column 6, lines 47-67 27, and 29).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the kit and method of and column 7, lines 1-52).

Hitomi et al, with monoclonal antibodies to the defensins HNP1-3 that can be prepared for an ELISA in 96-well plates, as taught by Heine et al, in order to screen a pregnant patient for the presence of an intraamniotic infection using amniotic fluid. One of ordinary Heine et al, in order to screen a pregnant patient for the presence of an intraammout infection using ammout fund. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in performing an ELISA on multiple antigens, as taught by Heine et al, in the kit and method of Hitomi et al, since Hitomi et al teach an ELISA kit and method using antibodies, and as taught by Heine et al., in the Mr. and themou of fortonin et al., Since fortonin et al teach an ELISA Kit and method using anubodies, and the 96-well plate taught by Heine et al is used for ELISA assays and can accommodate distinguishable binding assays between each of HNP-1 and calgranulin, and their respective antibodies in separate wells.

Claims 14 and 30 lack an inventive step under PCT Article 33(3) as being obvious over Hitomi et al (US 5,976,832), in Claims 14 and 30 fack an inventive step under PC1 Article 33(3) as being obvious over ritionin et at (0.5.3,970,032), in light of lig et al (Biochemical and Biophysical Research Communications, 1996, 225:146-150), and in view of Vogl et al (The Journal 1996, 225:146-150), and in view of Vogl et al (Polyment 1 ingni of lig et al (Biochemical and Biophysical Research Communications, 1990, 223:140-150), and in view of vogi et al (The Journal of Immunology, 1999, 163:2209-2216). ACBI CHEMISTY, בדקד, בואן, בואס בו מון במספר and rassey et al (The Journal of minimulology, במספר, 103.2207-2210).

Hitomi et al reference has been disclosed above, but fails to teach that said calgranhulin in the diagnostic assay is calgramilin

Vogl et al reference and Passey et al reference disclose binding of monoclonal antibodies to MRP8, in order to locate

WRP8, which is an important regulator of cytoskeletal/membrane interactions during phagocyte activation (Vogl et al: page 25291, MRP8, which is an important regulator of cytoskeletal/memorane interactions during phagocyte activation (vogi et al. page 25291, right column, 1st full paragraph), and which is a known regulator of inflammation that right column, 1- tuil paragraph; and page 25272, left column, 4- tuil paragraph), and which is a known regulated, wherein MRP8 is also is expressed at the critical time and place where infiltration of the embryo by maternal cells must be regulated, wherein MRP8 is also is expressed at the critical time and place where minuation of the emotyo by material cens must be regulated, wherein blure known as \$100A8 and calgranulin A (Passey et al. page 2209, left column, 1st paragraph, lines 11-13; and page 2215, 2st full

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the kit and method of Hitomi et al reference with binding of monoclonal antibodies to MRP8, in order to locate MRP8, which is an important regulator of rition et al reference with officing of monocronal and oodies to Micro, in order to locate Micro, which is an important regulato cytoskeletal/membrane interactions during phagocyte activation, as taught by Vogl et al and Passey et al, and which is a known paragraph, lines 34-37). cytoskeletai/memorane interactions during phagocyte activation, as laught by vogi et al and rassey et al, and which is a known regulator of inflammation that is expressed at the critical time and place where infiltration of the embryo by maternal cells must be regulator of inflammation that is expressed at the critical time and place where influention of the emoryo by maternal cells must be regulated, wherein MRP8 is also known as \$100A8 and calgranulin A. One of ordinary skill in the art at the time of the invention regulated, wherein Micro is also known as Stooms and calgrammin A. One of ordinary skin in the art at the time of the invention would have reasonable expectation of success in performing an assay on calgrammin A, as taught by Vogl et al and Passey et al, in the would have reasonable expectation of success in performing an assay on cargranum A, as taught by vogi et at and rassey et at, in kit and method of Hitomi et al, since Hitomi et al teach an ELISA kit and method using antibodies, and calgramilin A can also be

Claims 1-31 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed detected using antibodies. can be made or used in industry.

Claims 1-31 meet the control of the	
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new CITATIONS NEW CITATIONS NEW CITATIONS	, calgrammin C, Court
A mino acid sequence determination of financiations. 1996, 225	5:140-150.
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S spectrometry. Biochemical and Biophysical Research Communications. 1996, 225:146-150. Ilg, Evelyn C. et al. Amin

Form PCT/IPEA/409 (Continuation Sheet) (July 1998)